Advancing HIV Vaccines into Efficacy studies

Glenda Gray
WHO PD VAC
7-9 September 2015
Geneva, Switzerland
Innovations in Prevention that will be required when secondary transmission is not averted

HIV Cure: to enable control by eliminating viremia in those infected

What we need to end AIDS: controlling viremia

Transmission occurs sub-clinically

Gray, G et al Plos Biol, in press 2015
“Ultimately, we believe, the only guarantee of a sustained end of the AIDS pandemic lies in a combination of non-vaccine prevention methods and the development and deployment of a safe and effective HIV vaccine.”
Challenges for making HIV vaccines

• Scientific: highly variable virus that integrates into host genome, rapidly establishing latency, evading both humoral & cellular responses
Limited financial investment from Private Sector & LMIC countries

Limited pharmaceutical support

HIV PREVENTION R&D BY FUNDER TYPE 2013

- US Public Sector: 71%
- Other Governments: 5%
- European Public Sector: 15%
- Philanthropic: 3%
- Industry: 6%

Donaldson E, et al, HIVR4P 2014
This has resulted in only 4 vaccine concepts that have been tested in 6 efficacy trials in 30 years
<table>
<thead>
<tr>
<th>Study/Location</th>
<th>Vaccine/s</th>
<th>Risk Group/HIV Incidence</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Vax003 Thailand</td>
<td>AIDSVAX B/E gp120 in alum</td>
<td>IDUs 3.4%</td>
<td>No VE</td>
</tr>
<tr>
<td>1. Vax004 US/Europe</td>
<td>AIDSVAX B/B gp120 in alum</td>
<td>MSM/high risk women 2.6%</td>
<td>No VE</td>
</tr>
<tr>
<td>2. HVTN 502 Americas STEP</td>
<td>MRKAd5 HIV-1 gag/pol/jef</td>
<td>MSM/high risk women 3%</td>
<td>Halted for futility; early transient increased infection in vaccinees</td>
</tr>
<tr>
<td>2. HVTN 503 RSA Phambili</td>
<td>MRKAd5 HIV-1 gag/pol/jef</td>
<td>Heterosexual men &amp; women 3.7%</td>
<td>No VE; late increased HIV infection in unblinded male vaccinees</td>
</tr>
<tr>
<td>3. RV144 Thailand</td>
<td>ALVAC-HIV vCP1521, AIDSVAX B/E rgp120 in alum</td>
<td>Heterosexual men and women with variable risk 0.28%</td>
<td>31.2% VE @ 42/12; 60% VE @ 12/12</td>
</tr>
<tr>
<td>4. HVTN 505</td>
<td>DNA(gag/pol/jef/env) rAD5gag/pol/env (A,B,C)</td>
<td>Circumcised MSM Ad5 neg 1.8%</td>
<td>Halted at interim analysis for futility</td>
</tr>
</tbody>
</table>
Thai Trial (RV144) Primary Results

Vaccine efficacy decreases over time

<table>
<thead>
<tr>
<th>Time (mo)</th>
<th>Cumulative Infections</th>
<th>% HIV-1 infection rate (95% CI)</th>
<th>Cumulative Infections</th>
<th>% HIV-1 infection rate (95% CI)</th>
<th>Vaccine Efficacy (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>12</td>
<td>12</td>
<td>0.15 (0.07,0.24)</td>
<td>30</td>
<td>0.38 (0.24,0.52)</td>
<td>61</td>
</tr>
<tr>
<td>24</td>
<td>32</td>
<td>0.41 (0.27,0.55)</td>
<td>50</td>
<td>0.64 (0.46,0.82)</td>
<td>36</td>
</tr>
<tr>
<td>36</td>
<td>45</td>
<td>0.58 (0.41,0.75)</td>
<td>65</td>
<td>0.84 (0.63,1.04)</td>
<td>31</td>
</tr>
<tr>
<td>42</td>
<td>51</td>
<td>0.68 (0.49,0.87)</td>
<td>74</td>
<td>0.96 (0.74,1.18)</td>
<td>31</td>
</tr>
</tbody>
</table>

125 HIV infections in 16395 subjects

The NEW ENGLAND JOURNAL of MEDICINE

Vaccination with ALVAC and AIDSVAX to Prevent HIV-1 Infection in Thailand

Supachai Rerkas-Ngarm, M.D., Punnee Pitouttithum, M.D., D.T.M.H., Sorachai Nittayaphan, M.D., Ph.D., Jarant Kawkungwai, Ph.D., Joseph Chiu, M.D., Robert Paris, M.D., Nakorn Premchai, M.D., Chaweesak Hunwet, M.D., Mark de Souza, Ph.D., Elizabeth Adams, M.D., Michael Benenson, M.D., Sañy Gurunathan, M.D., Jim Tartaglia, Ph.D., John G. McNeil, M.D., Donald P. Francis, M.D., D.Sc., Donald Stabile, Ph.D., Deborah L. Birx, M.D., Supamit Chunsritattawat, M.D., Chirasak Khambhoruean, M.D., Prisert Thongchaeo, M.D., Ph.D., Merlin L. Robb, M.D., Nelson L. Michael, M.D., Ph.D., Prajupa Kurusoo, M.D., and Jerome H. Kim, M.D., for the MOPH-TAVEG Investigators
Kinetics of Vaccine-Induced Immune Response and Vaccine Protection Based on RV144

Levels

Limited/No Vaccine Protection

Poor Ab Response, T-cells

Good Vaccine Protection

Waning Vaccine Protection

Months

T-cells

Ab

0 1 3 6 9 12

Pox Pox Pox + Env protein Pox + Env protein Pox + Env protein

AIDS Vaccine Conference 2009, Bangkok
Key correlates that emerged from RV144 that appeared to be related to Vaccine Efficacy (Haynes, 2012)

- The binding of IgG antibodies to the V1V2 region of gp 120
- The binding of plasma IgA to env
- The avidity of IgG antibodies for env
- Antibody Dependent Cellular Cytotoxicity (ADCC)
- Neutralising Antibodies to vaccine antigen
- The magnitude of CD4 T cells specific for HIV-1 env

In vaccinees with low plasma IgA responses
Association between V1V2 antibodies and HIV acquisition in RV144 is critical to VE

A

B

0.010
0.008
0.006
0.004
0.002
0.000

0 12 24 36

Time since Week 26 visit (months)

Probability of Infection

Placebo
Low
Medium
High

Uninfected Placebo Low Medium High Uninfected Vaccine
V1/V2 IgG Correlate of Risk

- V2 Specific mAbs were isolated and characterized that involve position 169 in the V2 loop (Liao et al. Immunity 2013).


  ![Diagram of V2 Loop with 169 and 181 positions highlighted]

  - 60% of clade C isolates have lysine at position 169 vs 10% of clade B isolates
lack of a direct correlation between neutralising antibodies and HIV-1 acquisition

Even at peak antibody response, none of the sera from the vaccinees neutralised a panel of 20 contemporaneous isolates of HIV-1 circulating in Thailand during the course of the trial…..
Post RV144 world: conceptual summary of the correlates work

- Non neutralising antibodies with antibody functions such as ADCC, ADCP & virion capture, as well as polyfunctional CD4 T cell responses were associated with VE

- Neutralisation was not the mechanism that protected against HIV acquisition

- Strategies that build on these concepts have formed the basis of the efficacy studies taken forward
Besides non neutralising HIV vaccine approaches....other things were happening in the neutralising space
Immunogen design to induce neutralisation

• Advances in B cell technology have enabled the field to identify and isolate broadly neutralising antibodies from persons with chronic HIV infection.

• Passive transfer of these BNABS have demonstrated protection in NHPs from experimental challenge.

• Opening up a new vaccine approach either utilising these BNABS as passive immunisation or to form the basis of new immunogen design.
This leads us to evaluate 3 strategies to advance HIV immunization

- **P5 “Clade C” approach using ALVAC & gp120/MF59 (HVTN 702)**
- **Multi-clade approach using rAd26/MVA/gp140 trimer**
- **Neutralising antibody approaches**
Purpose:
To build on RV144 data and ultimately license a pox-protein based HIV vaccine with the potential for broad and timely public health impact.

Strategy:
Continue to build public-private partnerships critical for success.
1. Work with host countries to support a flexible regulatory strategy in target populations and regions.
2. Generate and incorporate knowledge from the assessment of next-generation vaccine concepts.
The Strategy for the ALVAC/Protein Phase 3 Program

Construction of Bivalent Subtype C gp120/MF59

Construction of ALVAC-HIV-C (vCP2438)

Optimize regimen by increasing potency and durability

Booster at 12 months
HVTN Strategy for the Phase 3 Program

HVTN 097
Designed to evaluate RV144 vaccine regimen in RSA and compare immunogenicity to that in Thailand

HVTN 100
A standard phase 1 trial of the clade C products to decide whether to proceed to phase 3

HVTN 702
A Classic phase 3 RCT assessing efficacy and safety aimed at licensure
Peak CD4\(^+\) T Cell Response Rates and Magnitudes are Higher in Prevalence in 097 vs. RV144

<table>
<thead>
<tr>
<th>Response rate:</th>
<th>RV144</th>
<th>HVTN 097</th>
<th>RV144</th>
<th>HVTN 097</th>
</tr>
</thead>
<tbody>
<tr>
<td>% T cells expressing IFN-(\gamma) and/or IL-2</td>
<td>50.3%</td>
<td>69.2%</td>
<td>2.5%</td>
<td>3.8%</td>
</tr>
<tr>
<td>Number</td>
<td>88/175</td>
<td>54/78</td>
<td>1/40</td>
<td>3/78</td>
</tr>
</tbody>
</table>

\(P = 0.01\) for RV144 vs. HVTN 097

\(P = 1.00\) for RV144 vs. HVTN 097

92TH023-ENV

LAI-GAG

Gray G HIVR4P, 2014
Comparison of V1V2 IgG responses between 097 and RV144
No significant difference seen in CD4+ T-cell responses for BMI, gender or age

<table>
<thead>
<tr>
<th>Stratum</th>
<th>Response rate</th>
<th>Response Rate %</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI &lt;25</td>
<td>33/50</td>
<td>66.00%</td>
<td>(52.2%, 77.6%)</td>
</tr>
<tr>
<td>BMI 25-30</td>
<td>15/19</td>
<td>78.90%</td>
<td>(56.7%, 91.5%)</td>
</tr>
<tr>
<td>BMI &gt;30</td>
<td>8/9</td>
<td>88.90%</td>
<td>(56.5%, 98.0%)</td>
</tr>
<tr>
<td>Female</td>
<td>28/37</td>
<td>75.70%</td>
<td>(59.9%, 86.6%)</td>
</tr>
<tr>
<td>Male</td>
<td>28/41</td>
<td>68.30%</td>
<td>(53.0%, 80.4%)</td>
</tr>
<tr>
<td>Age &lt;=20</td>
<td>18/24</td>
<td>75.00%</td>
<td>(55.1%, 88.0%)</td>
</tr>
<tr>
<td>Age &gt;20</td>
<td>38/54</td>
<td>70.40%</td>
<td>(57.2%, 80.9%)</td>
</tr>
</tbody>
</table>

Sites did adjust their needle length according to BMI
Study Schema: HVTN 100

<table>
<thead>
<tr>
<th>N (total 252)</th>
<th>Primary Vaccine Regimen</th>
<th>Booster</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Month 0</td>
<td>Month 1</td>
</tr>
<tr>
<td>210</td>
<td>ALVAC-HIV (vCP2438)</td>
<td>ALVAC-HIV (vCP2438)</td>
</tr>
<tr>
<td>42</td>
<td>Placebo</td>
<td>Placebo</td>
</tr>
</tbody>
</table>

Products:
- ALVAC-HIV (vCP2438) expressing HIV-1 env (clade C gp120), clade B (gp41), gag (clade B) & protease (clade B) (Dose: >1 X 10^6 CCID_{50})
- Bivalent subtype C gp120/MF59 containing 100mcg TV1.Cgp120 & 100mcg 1086.Cgp120

Immunogenicity evaluation to be applied to this study to inform advancement into phase 3: study fully enrolled in RSA
HIV vaccine trials offer a ray of hope

Breakthrough measure has the potential to stem the Aids pandemic that is ravaging SA

ZODILE MAPOKANDE

A HIV vaccine that has the potential to end the 6th epidemic in South Africa is currently being tested in the country.

If all goes well in the follow-up study set to begin late next year, the vaccine could be available for general use by 2015.

More than 200 people have been enrolled in the trial of MCV-019, which began in January and is expected to be completed by the end of this year.

The trial is being conducted by the HIV Vaccine Trials Network and the Medical Research Council.

Participants have been given a modified version of the so-called Th1 vaccine to test it for safety and ascertain whether the medicial regimen induces the required immune system responses.

The Th1 - or HIV - vaccine made headlines worldwide in 2009 when there was evidence that it could offer protection against HIV infection by up to 30% when used in Thailand. The findings were hailed as a breakthrough in the decades-long struggle to develop an effective vaccine.

The vaccine had to be used as part of a confirmatory trial in various parts of the world.

South Africa decided in 2011 to see whether South Africans would have the same immune response to MCV-019 as their counterparts in Thailand.

Trials were conducted at three sites: Germiston, Umgababa and Cape Town.

The reason for testing the immune response instead of its effectiveness is that HIV infection prevention is a physiological aspect such as genetic, age, obesity and body mass index, often affect individuals differently. Women, for instance, respond better to vaccines than men, while heavy drinkers and obese people don't respond as well.

The results of the 231 South African trial, MCV-019G, were promising. The immune response was low but, if not better, than that of the Thai, despite the differences in obesity and levels of glucose in the group of 100 people who participated in the local study.

TALK TO US
Is it still a stigma to live with HIV/AIDS?
SMS us at 39987 using the keyword HEV and tell us what you think. Please include your name. SMSes cost R1.50.

This set the stage in motion for the first phase of the trial currently under way, said Professor Linda-Gail Bekker of the Desmond Tutu HIV Centre at the University of Cape Town.

Speaking on the sidelines of the seventh South African Aids Conference in Durban last week, Bekker said the findings of the MCV-019 trial, which were released in November last year, were the best news South Africa had seen in terms of new initiatives that came to HIV prevention research.

"We are lucky to ask what the outcome of MCV-019 will be, but we are hoping to more than much the immune response noticed in the MCV-019 trials. If we do, we will keep ahead and continue phase two trials whose we will test the effectiveness of the vaccine. Phase two will be a large study that will include other African countries.

"The vaccine currently being tested has been modified to include different proteins that would trigger the HIV vaccine that was prevalent in South Africa.

"Bekker explained. "This vaccine that was used in our previous trial was targeted at strains 1 and 2, which are prevalent in Thailand. The Thai change their strain every year. These studies are critical to developing a strain that is prevalent in South Africa." The results of the trial are expected early next year.
Go/No-Go Criteria: HVTN 100 Must Meet all of the Following Conditions to advance to HVTN 702

<table>
<thead>
<tr>
<th>Parameters to be assessed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prevalence of Binding Antibodies to clade C gp120 antigens in the vaccine that approach 90%</td>
</tr>
<tr>
<td>Prevalence of V1V2 antibodies to clade C gp70 scaffold antigens of &gt;57% at week 28</td>
</tr>
<tr>
<td>CD4+ T cell responses to HIV env of ~60%</td>
</tr>
<tr>
<td>The above immune responses would, based upon RV 144 predict a VE=50% @ 2 years</td>
</tr>
</tbody>
</table>
### Study Schema: HVTN 702

<table>
<thead>
<tr>
<th>N (total 5400)</th>
<th>Primary Vaccine Regimen</th>
<th>Booster</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Month 0</td>
<td>Month 1</td>
</tr>
<tr>
<td>2700</td>
<td>ALVAC-HIV (vCP2438)</td>
<td>ALVAC-HIV (vCP2438)</td>
</tr>
<tr>
<td>2700</td>
<td>Placebo</td>
<td>Placebo</td>
</tr>
</tbody>
</table>

**Estimated Total Study duration 72 months:**
- Stage 1: 60 months-18 months for enrolment, 24 months of follow-up for HIV-1 uninfected individuals, 18 months follow up for HIV-1 infected individuals
- Stage 2: an additional 12 months of follow up for uninfected individuals
Timelines

**HVTN 100** Phase 1-2  \( n=252 \)
1. ALVAC/ALVAC-gp120
2. Placebo

**HVTN 702** Phase 3  \( n=5,400 \)
1. ALVAC/ALVAC-gp120
2. Placebo

- **Protocol Development**
- **RSA Regulatory Review**
- **Enrollment**
- **Follow-up**

**Timeline Events**
- Interim Safety Report
- Phase 3 Go/No Go Decision
- 1st – 3rd Efficacy/Futility Analyses
- Final Stage 1 Efficacy Analysis
# Target Product Profile

<table>
<thead>
<tr>
<th>Area</th>
<th>Base Case</th>
<th>Desired Up-side</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Indication</strong></td>
<td>Prevention of HIV infection</td>
<td></td>
</tr>
<tr>
<td><strong>Product</strong></td>
<td>Sanofi ALVAC recombinant canarypox prime containing HIV genes/ NVD bivalent Env protein with MF59</td>
<td></td>
</tr>
<tr>
<td><strong>Launch Date</strong></td>
<td>Earliest possible regional approval in Republic of South Africa (RSA) or Thailand</td>
<td>Fast-track review by regional authority WHO pre-qualification at launch; Article 58</td>
</tr>
<tr>
<td><strong>Target Population</strong></td>
<td>Primary: Seronegative adults at high risk for acquiring HIV infection</td>
<td>Inclusion of seronegative adolescents</td>
</tr>
<tr>
<td><strong>Efficacy</strong></td>
<td>≥ 50% reduction in laboratory confirmed HIV infection rate at 24 months after first administration</td>
<td>≥ 70% reduction in HIV infection rate</td>
</tr>
<tr>
<td><strong>Safety</strong></td>
<td>Well tolerated, adverse event profile comparable to standard adult vaccines.</td>
<td></td>
</tr>
<tr>
<td><strong>Dosage and Administration</strong></td>
<td>ALVAC: each dose contains &gt;10⁶ CCID₅₀ after reconstitution</td>
<td>Fewer doses, shorter dosing schedule (6 months), 50 mcg dose each Env protein</td>
</tr>
<tr>
<td></td>
<td>Env protein: bivalent recombinant Env protein with MF59 adjuvant, at a dose of 100 mcg of each Env protein</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Primary dosing: months 0 &amp; 1 ALVAC, months 3 &amp; 6 ALVAC and Env protein</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Booster: month 12 ALVAC and Env protein</td>
<td></td>
</tr>
<tr>
<td></td>
<td>All administrations will be intramuscular</td>
<td></td>
</tr>
<tr>
<td><strong>Protection</strong></td>
<td>Duration of protection 24 months from first administration</td>
<td>36 months from first administration</td>
</tr>
<tr>
<td><strong>Stability / Shelf Life</strong></td>
<td>At least 24 months</td>
<td></td>
</tr>
<tr>
<td><strong>Presentation / Formulation</strong></td>
<td>ALVAC: Lyophilized powder (stored at 2-8°C) and saline for injection.</td>
<td>1. All components stored 2-8°C</td>
</tr>
<tr>
<td></td>
<td>Env protein: 3 component vials (2 Env proteins stored -80°C; MF59 stored 2-8°C). Extemporary mixing of thawed proteins and MF59 adjuvant for a single injection</td>
<td>2. Single vial containing both Env proteins with MF59</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3. Multi-dose presentation</td>
</tr>
<tr>
<td><strong>Price &amp; COGS</strong></td>
<td>TBD</td>
<td></td>
</tr>
</tbody>
</table>
3 strategies to advance immunization

- P5 “Clade C” approach using ALVAC & gp120/MF59 (HVTN 702)
- Multi-clade approach using rAd26/MVA/gp140 trimer
- Neutralising antibody approaches
HIV vaccine research program: Janssen and Collaborators

IAVI  Ragon  NIAID/HVTN

BIDMC  Harvard  MHRP
HIV Vaccine Aiming at Protection Against all Clades of HIV-1

Different HIV-1 clades dominate in different geographic regions

Adolescents (11-17 years) / Adults (18-65 years) in endemic countries and populations at risk in Western world

1. Potent priming Vectors
   - Low seroprevalent Ad26
   - Ad26.HIV-Gag-Pol
   - Ad26.HIV-Env
   - (MVA.HIV-Gag-Pol-Env)

2. Mosaic inserts for global coverage

3. Trimeric env protein for improved humoral immunity

Mosaic HIV-1 vaccines expand the breadth and depth of cellular immune responses in rhesus monkeys

Dan H Barouch et al., 2013
A prime-boost vaccine regimen aiming at global coverage starting 2017-2021

Prime

Ad26 Mosaic vectors gag-pol-env

Ad26 Mosaic vectors gag-pol-env

Boost

Ad26 Mosaic vectors gag-pol-env

Soluble trimer gp140 env protein +/-

or

MVA Mosaic vectors gag-pol-env

Soluble trimer gp140 env protein +/-

Regimen to be selected after Phase 1/2a
Ad26/Env SIV Vaccines Partially Protect Against IR SIVmac251 Challenges in Rhesus Monkeys

90% reduction of per exposure acquisition risk for Ad/Env (P=0.001)
50% (6 of 12) show complete protection for Ad/Env (P=0.01)

• 32 rhesus monkeys
  • Ad26/Env (N=12)
  • Ad26/Ad35 (N=12)
  • Sham (N=7)

• Repetitive, intrarectal, heterologous SIVmac251 challenges

• Correlates of protection
  • ELISA  P < 0.0001
  • Ab Funct  P = 0.004
  • NAb  P = NS

Barouch et al. Science 2015
3 strategies to advance immunization

- P5 “Clade C” approach using ALVAC & gp120/MF59 (HVTN 702)
- Multi-clade approach using rAd26/MVA/gp140 trimer
- Neutralising antibody approaches
Neutralising Ab to HIV-1

- V1V2-Glycan – bind to trimer cap
- V3-glycan, N332 supersite
- gp41 MPER – near membrane
- gp120/41 interface – bind to parts of both gp120 and gp41
- CD4 binding site of gp120 – where the virus attaches to CD4

Only antibodies that have advanced to the clinic (VRC01, 3BNC117)
Use of HIV Antibodies in Prevention

- Can mAb prevent infection in high risk adults (Antibody Mediated Prevention)

- Can mAb protect infants during childbirth and breastfeeding

- Can we use it as a topical microbicide?

- What level of antibody is needed (ug/ml) to protect

- How long will the antibody work (weeks, months?)

- Cocktails to increase breadth vs potency
## Neutralisation Activity of VRC01

<table>
<thead>
<tr>
<th>Virus clade</th>
<th>Number of viruses</th>
<th>IC$_{50}$ &lt; 50 µg/mL</th>
<th>IC$_{50}$ &lt; 1 µg/mL</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>22</td>
<td>100%</td>
<td>95%</td>
</tr>
<tr>
<td>B</td>
<td>49</td>
<td>96%</td>
<td>80%</td>
</tr>
<tr>
<td>C</td>
<td>38</td>
<td>87%</td>
<td>66%</td>
</tr>
<tr>
<td>D</td>
<td>8</td>
<td>88%</td>
<td>50%</td>
</tr>
<tr>
<td>CrRF01_AE</td>
<td>18</td>
<td>89%</td>
<td>61%</td>
</tr>
<tr>
<td>CRF02_AG</td>
<td>16</td>
<td>81%</td>
<td>56%</td>
</tr>
<tr>
<td>G</td>
<td>10</td>
<td>90%</td>
<td>90%</td>
</tr>
<tr>
<td>CRF07_BC</td>
<td>11</td>
<td>100%</td>
<td>45%</td>
</tr>
<tr>
<td>Other</td>
<td>18</td>
<td>83%</td>
<td>78%</td>
</tr>
<tr>
<td>Total</td>
<td>190</td>
<td>91%</td>
<td>72%</td>
</tr>
</tbody>
</table>
VRC01 Protects against Mucosal SHIV-Challenge in Non-human Primates

20 mg/kg infusion of VRC01: Challenge with SHIV SF162P3

RECTAL CHALLENGE

VAGINAL CHALLENGE

4/4 protected

0/4 protected

4/4 protected

1/4 protected

All the NHP studies are with cell free virus, in humans we know that there is cell associated sexual and breast milk HIV transmission.
Passive Antibody Prevention

- NHP studies tell us that physiologically achievable levels of Ab could prevent HIV-1 infection: *But no direct proof in humans*

- Need to Learn from Proof of Concept in Humans and understand the mechanism in which bNABs protect against infection

- Antibody Mediated Prevention trial (HVTN/HPTN) in MSM (clade B) & heterosexual women (clade C) starting in 2016
HVTN 703 / HPTN 081

• A phase 2b trial to determine if intravenous (IV) administration of VRC01 as a means of preventing HIV-1 acquisition in two high risk populations:

  • (1) men who have sex with men (MSM) and transgender women who engage in high risk sexual behavior in the US and South America (Clade B).

  • (2) women in Sub-Saharan Africa (Clade C) who are at high risk of HIV acquisition through heterosexual sex.

• These populations have been selected because of VRC01’s capacity to neutralize a broad range of both Clade C and Clade B viruses and because levels of antibodies required for protection from acquisition may vary by anatomic site and type of sexual exposure.
<table>
<thead>
<tr>
<th>Cohort</th>
<th>Treatment</th>
<th>N</th>
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<th>16</th>
<th>24</th>
<th>32</th>
<th>40</th>
<th>48</th>
<th>56</th>
<th>64</th>
<th>72</th>
<th>80*</th>
<th>92†</th>
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</thead>
<tbody>
<tr>
<td>Group 1</td>
<td>VRC01 10 mg/kg q8 weeks</td>
<td>800</td>
<td>A</td>
<td>A</td>
<td>A</td>
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<tr>
<td>North + South American MSM &amp; TG</td>
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<td>Group 5</td>
<td>VRC01 30 mg/kg q8 weeks</td>
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</table>

* No infusion; last study visit for the primary analysis of treatment efficacy.
† 12 weeks off-treatment follow-up for secondary analyses and for the co-primary objective of evaluating safety and tolerability; Week 92 is the terminal study visit.

TG = male-to-female and female-to-male transgender persons.
The critical link between AMP & immunogen design will be in defining the levels of neutralisation required to achieve protection and will set the standard for developing immunogens that achieve these levels of antibodies.
What we need to remember
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